Summary of Panel Discussions

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Introduction

During the Workshop "Pharmacokinetics: Defining the Dose for Risk Assessment," two panel discussions were held. The first was "Design of Studies to Obtain Pharmacokinetic Data for Risk Assessment." Emil Pfitzer of Hoffmann-La Roche, Inc.; James Stevens of Ciba-Geigy Corporation;Penelope Fenner-Crisp of the U.S. Environmental Protection Agency Pesticides Program; and Daniel Menzel of the University of California, Irvine, were lead discussants. The second was "How Pharmacokinetics Affects Risk Assessments in Sensitive Populations, Especially the Very Young and the Elderly" with Daniel Krewski of the Health and Welfare Canada, John Doull of the University of Kansas, Alan Wilson of Monsanto Company, and Donald Mattison of the University of Pittsburgh as lead discussants.

The discussions centered around the following four questions: *a*) What pharmacokinetic data are needed for risk assessment? *b*) When should pharmacokinetic data be obtained in toxicity testing? *c*) How can pharmacokinetic data be applied in risk assessment? *d*) How is pharmacokinetics altered in sensitive populations?

What Pharmacokinetic Data Are Needed for Risk Assessment?

Pharmacokinetic studies of pesticides need to be designed to determine what happens from the time a person comes into contact with a pesticide via its most common route of exposure until the body's response to the pesticide is completed. Such studies provide information on the uptake, distribution, metabolism, and elimination of pesticides in the body and on the dose of toxic metabolites reaching target tissues. Once the disposition of low doses of a compound is established, the effect of increasing dose on distribution patterns and excretion routes needs to be determined. Of particular interest is the saturation of metabolic pathways leading to a nonlinear relationship between the level of exposure and the dose to the target tissue. Doses that are lower than those exceeding the total metabolic capacity of the host might still be high enough to cause shifts in metabolic pathways from low capacity and high affinity enzymes to high capacity and low affinity enzymes. Such shifts might greatly influence the toxic effects exerted by the compound, depending on the kinetic characteristics of the pathway leading to formation of the toxic metabolite. Information on the disposition of a compound as a function of dose is essential for evaluating risks to humans exposed at low doses on the basis of the results of animal toxicity studies conducted at high doses.

The effect of repeated dosing on the distribution, metabolism, and excretion of the compound needs to be determined to evaluate the risks of individuals subject to multiple exposures over time properly. These studies are necessary to take into account the possibility of the induction of enzymes to either increase or decrease the level of toxic metabolites. Other dose–rate effects such as accumulation of lipid-soluble metabolites in fatty tissues can also be evaluated in repeated dosing studies.

Basic pharmacokinetic studies, which are generally conducted in animal models, need to be done with careful attention to mass balance. When studying the disposition of a pesticide, all of the material that entered the animal needs to be accounted for, either by retention in tissues or by excretion. Thus, all tissues and excreta should be analyzed for the presence of the administered compound or its metabolites. Whole-body radiography can be used to detect small amounts of radiolabeled material in small organs that might not always be analyzed.

A major point of discussion was the consensus tier approach to pharmacokinetic studies developed by the Synthetic Organic Chemical Manufacturers Association's Pharmacokinetics Group and presented by Alan Wilson. There was some concern about putting off identification of metabolites until tier three, although others stated that it was logical to determine whether metabolism of the substance occurs before attempting to determine the identity of metabolites. In general, the tier approach was considered appropriate as long as it is implemented with sufficient flexibility to take into account different informational needs for different materials.

When Should Pharmacokinetic Data Be Obtained in Toxicity Testing?

Two approaches for using pharmacokinetic data were discussed. One approach was using pharmacokinetic data for study design; the other was using such data for interpretation of already completed studies. The advantage of doing pharmacokinetic studies early (say in parallel with short-term toxicity studies) is that the effects of dose on the uptake and metabolism of the compound of interest will be known before setting exposure levels for long-term studies. Also, secondary mechanisms such as those described by Eldridge can be detected in time to avoid the use of an inappropriate animal model in long-term studies. For example, if pharmacokinetic studies indicated that a shift in metabolism resulting in a marked increase in the formation of toxic compound occurred at higher doses, it would be desirable to include an appropriate number of animals below that saturation point in long-term studies. If pharmacokinetic data in inhalation studies indicated that the dose to the target tissue did not increase because of a decrease in respiration rate or absorption above a certain exposure concentration, higher exposure concentrations would not be needed in the long-term studies.

The discussants who favored doing pharmacokinetic studies to aid in interpre-

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tation of the results from previously completed toxicity studies observed that detailed pharmacokinetic studies would not be helpful if toxicity was not observed. If a nonlinear dose–response relationship is observed for important toxic end points, then pharmacokinetic studies can be initiated to determine if the response is the result of saturation of metabolic pathways. Pharmacokinetic studies could be focused on metabolites in target organs identified in long-term toxicity studies.

How Can Pharmacokinetic Data Be Applied in Risk Assessment?

A major point of discussion was how pharmacokinetic data obtained from manufacturers of pesticides might be used by regulatory agencies. Some participants questioned whether or not the data would be used at all. One discussant pointed out that if the linearized multistage model is used as a dose–response model for carcinogenesis, internal-dose considerations are easily incorporated into the model for risk assessment purposes. Representatives of the U.S. EPA Pesticides Program pointed out that their institutional philosophy was to go beyond the series of default assumptions concerning mechanisms that are used in risk assessment and reflect biological reality based on scientific knowledge. Therefore, pharmacokinetic data would be useful in the regulatory process. A standardized approach to pharmacokinetic studies such as the consensus tier approach would be helpful for regulatory applications of pharmacokinetic data. However, concerns about the additional costs of such studies were raised. Others pointed out that the costs of obtaining pharmacokinetic data were much smaller than long-term chronic studies, and the data provided essential information for designing or interpreting chronic studies.

Representatives of pharmaceutical companies identified five types of pharmacokinetic data that are normally used to assess drugs. These are bioavailability, dose proportionality, the effect of repeated dosing, metabolism of the compound, and the relationship between blood or tissue levels and toxicity. This information is needed to evaluate the effects of pesticides as well as drugs, although assessment is more difficult for pesticides than for drugs. For pharmaceutical agents, scientists know exactly how much of the agent is administered and they can go quickly from preclinical studies to studies in humans. Detailed studies in humans are not possible for pesticides. There is also a defined route of exposure for pharmaceutical agents: people can be exposed to pesticides via ingestion, dermal absorption, and inhalation.

Mathematical models were considered by panelists to be a powerful tool for application of pharmacokinetic data. Models describing the pharmacokinetics of chemicals can be developed in animals and, with appropriate scaling techniques, can be used to predict the pharmacokinetic behavior of the same compound in humans. Biologically based models, which include appropriate physiological, biochemical, and metabolic parameters, provide a useful framework for describing the kinetics of distribution of a compound or its metabolites in the body. Such physiologically based pharmacokinetic models sometimes are most useful when the data do not fit the model. In this case, the investigator must try to determine what is missing from the model and develop a modified model that adequately describes the data. The exercise of model building and model refinement often provides useful insight into pharmacokinetic processes involved in the handling of xenobiotics by the body. In the work by Gearhart et al., the modeling process was carried one step further by melding the modeling of pharmacokinetic and pharmacodynamic data. They indicated that such an integrated biologically based modeling approach can provide a more complete description of the sequence of events leading to a toxic response to pesticide exposure.

How is Pharamacokinetics Altered in Sensitive Populations?

The panelists discussed the differences between children and adults in exposure to pesticides and in the rate of metabolism or clearance of the compound. Children are exposed to different amounts of pesticides by ingestion than are older persons. Studies at the University of Pittsburgh indicate that human breast milk is more contaminated with pesticides than cow's milk, although the degree of contamination of breast milk has gone down since 1986 (*1*). On a body weight basis, children are known to eat or drink more of certain foods or beverages such as apple juice than adults do (Figure 1). Therefore, in determining the potential dosimetry of children to pesticide-contaminated food, the increased intake of certain food products in children must be considered.

Information from studies on blood levels of administered cancer chemotherapeutic agents, such as those conducted at St. Jude's Hospital as reported by Crom, indicates that children metabolize and clear xenobiotics faster than adults. That also has been documented in a 1992 report from the International Life Sciences Institute entitled Similarities and Differences in Children and Adults: Implications for Risk Assessment. One discussant referred to the work of an Interagency Pharmacokinetics Group, a consortium of scientists from the Food and Drug Administration; the EPA; Consumer Product Safety Commission;

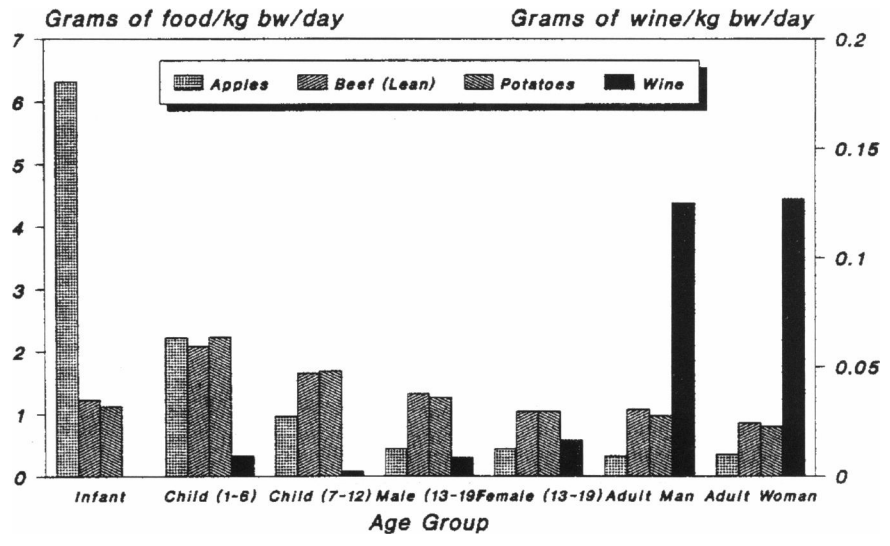

Figure 1. Body weight-adjusted food consumption (data from U.S. EPA's Tolerance Assessment System, based on USDA survey). USDA (U.S. Department of Agriculture). 1983. Nationwide Food Consumption Survey. Nutrient Intakes: Individuals in 48 States, Year 1977–78. Report No. I-1. Hyattsville, MD: Consumer Nutrition Division, Human Nutrition Information Service.

and the Occupational Safety and Health Administration, who reported that the ratio of liver to body weight is high in children. Thus, children may clear some chemicals faster than adults because clearance of some drugs is dependent on total liver mass.

Another factor that must be taken into account is the nutritional status of exposed people. It is well known that undernourished children or elderly persons have a decreased ability to mount and maintain normal immune response and thus they respond poorly to vaccination procedures that are effective in well-nourished children. Undernourished people also have less defense against toxic materials than well-nourished individuals because of decreased host defense mechanisms.

REFERENCES

1. Mattison DR, Wohlleb J, To T, Lamb Y, et al. Pesticide concentrations in Arkansas breast milk. J Ark Med Soc 88(11):553–557 (1992).